ATTACHMENT D
Amendments to the Drawings

The attached Replacement sheets of drawings include the following changes:

The respective four sheets for Figures 9-12 have been relabeled Fig. *x*A-*x*D; and the original French labels of Figs. 9-12 have been changed from "souris" to "mouse" (Figs. 9-11) and from "homme" to "human" (Fig. 12).

ATTACHMENT A

Remarks

Claims 1, 3, 4, 6, 7, 9, 10, 15, 20-22, 30 and 33-38 are pending in the present application. By this Amendment, Applicants have amended claims 10, 30 and 36 and added new claims 37 and 38. Applicants respectfully submit that the present application is in condition for allowance based on the discussion which follows.

Claims 1, 9, 10, 20, 21, 30 and 36 were rejected under 35 U.S.C. § 102(b) as being anticipated by Honnorat *et al.* (*J. Neurol. Neurosurg. Psych.* 1996; 61:270-278) (hereinafter "Honnorat *et al.* (1996)") as evidenced by Honnorat *et al.* (*Eur. J. Neurosci.* 1999 Dec.; 11(12):4226-4232) (hereinafter "Honnorat *et al.* (1999)").

As an initial point, it is improper to infer enablement from the teachings of Honnorat *et al.* (1996) using the teachings of Honnorat *et al.* (1999), as Honnorat *et al.* (1999) is not prior art of the present application under 35 U.S.C. § 102(b) since the present application has a priority date of February 19, 1997 and a U.S. filing date of August 17, 1999, both which precede the December 1999 publication date of Honnorat *et al.* (1999).

Honnorat *et al.* (1996) teaches that 9 of 11 serum samples from patients with paraneoplastic neurological syndromes (PNS) contained antibodies that bound to one or more proteins with an apparent molecular weight of approximately 66 kDa found in human embryo brain. Six of the 11 serum samples contained antibodies that bound to one or more proteins with an apparent molecular weight of approximately 66 kDa protein found in adult human brain. See Honnorat *et al.* (1996), page 275, second paragraph; data not shown.

Honnorat *et al.* (1996), Figure 7B (page 276) shows that the serum of one patient ("patient 2") contained antibodies that bound to proteins in an S3 fraction of human fetal brain (lane c) and to proteins in an S3 fraction of human brainstem (lane d). The proteins had been subjected to SDS polyacrylamide gel electrophoresis and transferred to an Immobilon membrane. Figure 7B shows an immunoperoxidase stained Western blot with diffuse bands migrating at a position of what can only be estimated as approximately 66 kDa.

Honnorat *et al.* (1996) did not characterize these proteins beyond estimating an apparent molecular weight of 66 kDa from their migration by SDS polyacrylamide gel electrophoresis. Honnorat et al. (1996) provided no amino acid sequence information or other structural information. With the exception of the limited teachings on the human proteins described above, Honnorat *et al.* (1996) described studies using rat proteins.

Honnorat *et al.* (1999) show an amino acid sequence of human Ulip4/CRMP3. In situ hybridization of metaphase human lymphocytes was carried out using the entire insert of the human Ulip4/CRMP3 cDNA alone as a probe. The gene was mapped to chromosome 10. The rest of Honnorat *et al.* (1999) describe experiments with rat proteins.

The Examiner is using the present specification as a reference as Honnorat *et al.* (1999) is essentially the same as the present specification, having been authored by the present inventors. The Examiner, in pointing out teachings of Honnorat *et al.* (1999), could just as easily have pointed out the same teachings by page and line in the present specification. Whatever reasons Honnorat *et al.* (1999) is being used for in the rejection are irrelevant. The teachings the Examiner has cited in Honnorat *et al.* (1999) are the

teachings of the specification. The specification is not a reference available for use in rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103 and the rejection is not permissible.

In the Office Action of 6 April 2005 (page 8, lines 3-12), the Examiner invoked the doctrine of inherency:

> In this instance, the claims are directed to a polypeptide comprising the amino acid sequence set forth as SEQ ID NO:8. While Honnorat *et al.* (1996) does not teach the amino acid sequence of the isolated and purified 66 kDA polypeptide, the amino acid sequence of a protein is an inherent characteristic. Honnorat *et al.* (1999) provides factual evidence that the protein isolated by Honnorat *et al.* (1996) is the same as the protein that is described by Honnorat *et al.* (1999). Because the protein described by Honnorat *et al.* (1999) comprises an amino acid sequence that is identical to SEQ ID NO:8, it would be recognized by persons of ordinary skill in the art that the protein isolated by Honnorat *et al.* (1996) necessarily has the amino acid sequence set forth as SEQ ID NO:8.

The Examiner has stated previously (page 25, lines 17-20 of Office Action of 22 November 2004):

> As evidenced by Honnorat *et al.* (1999), the 66 kDa polypeptide of Honnorat *et al.* (1996), which is endogenous to human brain cells, and to which anti-CV2 antibodies bind, is a polypeptide that comprises an amino acid sequence that is identical to SEQ ID NO:8; see entire document (e.g., the abstract; page 4230, Figure 5).

It should be noted that whenever a rejection under 35 U.S.C. § 102 is made that invokes the doctrine of inherency, the Examiner must provide a rationale or evidence tending to show inherency. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. App. &

Inter. 1990) (emphasis in original). See also *The Manual of Patent Examining Procedure* (revised August 2005) ("MPEP") 2112 (IV).

Applicants do not find that the Examiner has given evidence or reasoning necessarily linking the teachings of Honnorat *et al.* (1996) with the teachings of Honnorat *et al.* (1999). The Examiner has stated mere conclusions without identifying any basis in fact and/or technical reasoning.

Further, it should be noted that for a characteristic to be inherent in the prior art, that conclusion must necessarily flow from the teachings of the applied prior art.

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. US Inc. v. Monsanto Co.*, 20 USPQ2d 1746 at 1749 (CAFC 1991), quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

It is further quoted in *Continental Can Co. US Inc. v Monsanto Co.*:

> Inherency, however may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. *Hansgirg v. Kemmer*, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939).

The Examiner has presented insufficient reasoning to establish that the proteins of Honnorat *et al.* (1996) and Honnorat *et al.* (1999) are the same and that the protein of Honnorat *et al.* (1996) has an amino acid sequence of SEQ ID NO:8. The Examiner has not gone beyond the speculation that this may result from the set of circumstances presented.

The Examiner states (Office Action of 23 November 2005, page 4, lines 24-30):

> The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish

> that the product of the prior art does not possess the same material, structural and functional characteristics as the claimed nucleic acid. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed nucleic acid molecule is different than that taught by the prior art. See *In re Best*, 562 F.2d. 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (Bd. Pat App Int 1988, 1989).

In *In re Best*, claims to a crystalline zeolitic aluminosilicate were rejected under 35 U.S.C. §102 or 35 U.S.C. §103. Referring to *Ludtke*, the court in *Best* stated: "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. *In re Best*, 195 USPQ 430, 433 (CCPA 1977).

Note that section 2112 (V) of the MPEP begins: "Once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference."

In the case before us, the Examiner has <u>not</u> stated the reasoning as to why the claimed and prior art compositions are identical or substantially identical, or how they were produced by substantially identical procedures. Unless this is done, the Examiner has failed to establish a *prima facie* case of anticipation and the burden of proof that the compositions of the claims and the prior art are different cannot be properly shifted to the applicants.

The Examiner states that "the only relevant question to ask is, does the prior art anticipate the claimed invention?" This is not the only question to be considered. There

is a threshold issue to be considered first. Any prior art cited under 35 U.S.C. § 102(b) must first be assessed for whether it provides an enabling description of the invention. That is, would one of ordinary skill in the art be able to make and use the invention, given the description in Honnorat *et al.* (1996)?

Honnorat *et al.* does not provide a description of what it is purported to teach, a purified ULIP polypeptide comprising SEQ ID NO:8. Honnorat *et al.* (1996) does not provide enough information such that one of ordinary skill in the art would be able to produce a human protein that migrates on an SDS polyacrylamide gel with an apparent molecular weight of approximately 66 kDa protein and know that it is the same protein as that described in the paper. Honnorat *et al.* (1996) does not include sufficient information to identify the protein. Therefore, Honnorat *et al.* (1996) fails to be an anticipatory reference of the present application in accordance with *Elan Pharm, Inc. v. Mayo Found.*, 68 USPQ2d 1373 (Fed.Cir. 2003), as Honnorat *et al.* (1996) fails to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation. Without the present specification and Honnorat *et al.* (1999), one of ordinary skill in the art would not be enabled to practice the present invention as claimed. As Honnorat *et al.* (1996) does not include an enabling description of a polypeptide comprising amino acid sequence SEQ ID NO:8, Honnorat *et al.* (1996) is not an anticipatory reference and, therefore, it is not appropriate to cite it in a rejection based on 35 U.S.C. § 102(b).

The Examiner has cited *In re Best* and *Ex parte Gray* as demonstrating that the burden of proof shifts so that Applicants must prove that the compositions of the claims

and of the prior art differ. The issues in the cases cited by the Examiner are different from the issues presented in this case.

In *In re Best*, claim 1 of appellants' recited 6 parameters: SiO2/Al2O3 ratio, Na2O/Al2O3 molar ratio, cubic unit cell size, ion exchange capacity, oxygen adsorption capacity, and X-ray powder diffraction pattern. The prior art reference disclosed SiO2/Al2O3 ratio and Na2O/Al2O3 molar ratio within the ranges recited in claim 1. The other parameters were not specifically disclosed in the prior art reference. In *Best*, there was sufficient information in the prior art (i.e., an enabling description) to establish that the chemical composition of the claimed product and the prior art product were the same or substantially the same. The other parameters recited in claim 1 were characteristics dependent on the chemical composition.

The cited reference Honnorat *et al.* (1996) does not provide a description of a protein of SEQ ID NO:8. There is insufficient structural information in the Honnorat *et al.* (1996) reference to determine whether the chemical composition of a purified ULIP polypeptide comprising SEQ ID NO:8 of the claims and the approximately 66 kDa proteins on the gel in Honnorat *et al.* (1996) are the same or substantially the same. Therefore, *In re Best* cannot be applied to say that Applicants have the burden of proof to show that the claimed polypeptide has properties that are different from those of the protein of the prior art.

Ex parte Gray considered an issue of obviousness of the product in product-by-process claims. In that case, prior art publications described human nerve growth factor purified from human tissues. The claims were drawn to human nerve

growth factor free of other human proteins, as produced in cultured cells. In that case, human nerve growth factor had been identified as such in the prior art.

In the present application, there is insufficient information provided in the cited reference Honnorat *et al.* (1996) to identify the protein to which the Examiner refers. The human proteins that migrated on the SDS polyacrylamide gel with an apparent molecular weight of 66 kDa had been extracted from human brain tissue. See Figure 7B. The proteins were observed to bind to antibodies present in the serum of one patient ("patient 2") with paraneoplastic neurological syndrome. No activity was known for the proteins. No structural information was available for the proteins, beyond an apparent molecular weight on SDS polyacrylamide gel electrophoresis. The serum of patient 2 said to contain anti-CV2 antibodies contains many different antibodies that could bind to many different proteins. It cannot be said that "anti-CV2 antibodies" specifically recognize only that protein of apparent molecular weight 66 kDa, as it can be said for antibodies prepared by immunization of an animal with a purified protein. Therefore, no antibody preparation was described in Honnorat *et al.* (1996) that could be used to identify a protein.

Based on the foregoing, Applicants respectfully request that the rejection to claims 1, 9, 10, 20, 21, 30 and 36 under 35 U.S.C. § 102(b) as being anticipated by Honnorat *et al.* (1996) as evidenced by Honnorat *et al.* (1999) be withdrawn.

Claims 30 and 36 were rejected under 35 U.S.C. § 102(b) as being anticipated by Antoine *et al.* (*J. Neurol. Sci.* 1993; 117(1-2):215-223) as evidenced by Honnorat *et al.* (1999).

Antoine *et al.* describe tests of serum from a woman with paraneoplastic encephalomyelitis and undifferentiated carcinoma. The serum contained antibodies to proteins of 44, 59 and 135 kDa in extracts of human cerebellum, according to the results of western blot experiments. See page 220, section subtitled "Western blot." Figure 2G of Antoine *et al.* shows indirect immunofluorescence testing of the woman's serum on fixed human brainstem and cerebellum. The result was staining of "rare immuno-positive cells with small cytoplasm and short processes." See page 219, section subtitled "Human brain."

In Honnorat *et al.* (1999), a human EST homologous to the mouse Ulip4/CRMP3 cDNA was found in a database search, the gene for the human homolog was sequenced, and the human Ulip4/CRMP3 was mapped to chromosome 10.

The Examiner has cited Honnorat *et al.* (1999) in concluding that "fixed sections of human brain comprise an endogenous 66 kDa polypeptide, which comprises the amino acid sequences set forth as SEQ ID NO:8, to which anti-CV2 antibodies bind." This is a conclusion reached by using the teaching of the present specification that human Ulip4 has amino acid sequence SEQ ID NO:8. Use of the specification in rejections based on 35 U.S.C. § 102 and 35 U.S.C. § 103 is not permitted. The prior art fails to teach or suggest the amino acid sequence of human Ulip4, let alone, that human Ulip4 has the amino acid sequence of SEQ ID NO:8.

Further distinguishing the present invention from the prior art, claims 30 and 36 have been amended. As amended, claims 30 and 36 are drawn to reagents comprising purified polypeptides or purified peptides attached to a solid support. Neither Antoine

et al. nor Honnorat *et al.* (1999) describe purified polypeptides or purified peptides of all or part of SEQ ID NO:8 attached to a solid support.

Based on the foregoing, Applicants respectfully request that the rejection to claims 30 and 36 under 35 U.S.C. § 102(b) be withdrawn.

Claims 3, 6, 7, 15, 22 and 33-35 have been rejected under 35 U.S.C. § 103(a) as being obvious over Honnorat *et al.* (1996) as evidenced by Honnorat *et al.* (1999) further in view of US Patent No. 6,455,267 (hereinafter "'267").

The teachings of Honnorat *et al.* (1996) and of Honnorat *et al.* (1999) have been described above.

The '267 patent describes the cloning of cDNA encoding glutamic acid decarboxylase (GAD) and the use of GAD protein in the identification of autoantibodies to GAD present in the sera of diabetic patients.

With regard to claims 3, 6 and 7, the Examiner states (Office Action of 23 November 2005, page 7, lines 19-25):

> The Examiner has reasonably concluded that the isolated polypeptide disclosed by the prior art is the same as that which is claimed, since the isolated polypeptide has a molecular mass of 66 kDa, as does the claimed polypeptide comprising the amino acid sequence of SEQ ID NO:8. The prior art teaches the isolated polypeptide binds to anti-CV2 antibodies, as does the claimed polypeptide comprising the amino acid sequence of SEQ ID NO:8. The prior art teaches the isolated polypeptide is present in human brain, as is the claimed polypeptide comprising the amino acid sequence of SEQ ID NO:8.

The Examiner is respectfully requested to point out where he has found passages in the specification that state that the <u>human</u> polypeptide referred to in claim 3 has a molecular mass of 66 kDa and is known to be present in the human brain.

The Examiner continues (Office Action of 23 November 2005, page 7, lines 25-30):

> This conclusion [that the polypeptide of Honnorat *et al.* (1996) is the same as the polypeptide of the claims having SEQ ID NO:8] is further supported by the disclosures of the evidentiary reference, namely Honnorat *et al.* (1999). Honnorat *et al.* (1999) teaches some of the same results presented had already been reported in full detail in other publications, including, in particular, Honnorat *et al.* (1996); see, e.g., page 9, column 1. It is thus apparent that the studies disclosed by Honnorat *et al.* (1999) are extensions of those studies disclosed by Honnorat *et al.* (1996).

Applicants do not see the relevance of this. The issue is obviousness, the presence or absence of which is determined through an analysis of the differences between the claimed invention and what is found in the prior art.

Moreover, as stated above, Honnorat *et al.* (1999), is not prior art of the present application, as the present application has a priority date prior to the publication date of Honnorat *et al.* (1999). Honnorat *et al.* (1999), published after the filing date of the application, describes the work of the inventors, and to a large extent shares the content of the application. Thus, the Examiner is using the teaching of the application itself, which is never proper alone or in any combination with other art.

The Examiner has stated (Office Action of 22 November 2004, page 31, lines 24-30):

> Furthermore, it would have been prima facie obvious to one ordinarily skilled in the art at the time of the invention to produce a host cell transfected with a vector comprising a polynucleotide sequence encoding the polypeptide disclosed by Honnorat *et al.*, because '267 teaches such host cells can be used to produce the polypeptide. One ordinarily skilled in the art at the time the invention was made would have been motivated to make and use such kits [isolated nucleic acids, vectors and host cells?] to facilitate the production of the polypeptide for use in making the diagnostic kits.

The Examiner has concluded that the diffuse band at the position of proteins with approximate molecular weight 66 kDa, and bound to antibodies in serum from "patient 2" is necessarily one protein and the same protein discussed in Honnorat *et al.* (1999) and has amino acid sequence SEQ ID NO:8.

The Federal Circuit set forth the standards for anticipation by inherency:

> A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. *Lewmar Marine, Inc. v. Barient Inc.*, 827 F.2d 744, 747 [3 USPQ2d 1766] (Fed. Cir. 1987). Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 [20 USPQ2d 1746] (Fed.Cir. 1991).

It is an inherent feature of proteins that they have an amino acid sequence. It is not an inherent feature (that is, it is not necessarily a feature) of every brain protein that migrates as a band of approximately 66 kDa by polyacrylamide gel electrophoresis that it must have SEQ ID NO:8 as its amino acid sequence. Honnorat *et al.* (1996) discloses no more than a diffuse band on a gel migrating at an apparent molecular weight of approximately 66 kDa. The band very likely contains several proteins. The Examiner has not stated sufficient evidence or reasoning to establish a *prima facie* case of inherency.

The Examiner has found further motivation to produce the 66 kDa polypeptide of Honnorat *et al.* (1996) recombinantly, and in the process, to produce the claimed invention. The Examiner has referred to page 277, column 2 of Honnorat *et al.* (1996) (Office Action of 6 April 2005, page 9, lines 17-21). There, the authors are referring to the protein found in rat brain.

The Examiner again relies on Honnorat *et al.* (1999) for the conclusion that in the 66 kD band of human brain proteins which bound antibodies from "patient 2" in Honnorat *et al.* (1996) is a protein with amino acid sequence SEQ ID NO:8. Honnorat *et al.* (1999) lacks the teachings to make possible an identification of a 66 kDa human brain protein of Honnorat *et al.* (1996) as a protein with amino acid sequence SEQ ID NO:8. Without knowledge of the amino acid sequence SEQ ID NO:8, it would not have been possible to describe the inventions of claims 3, 6 and 7, no matter which other references Honnorat *et al.* (1996) is combined with. Honnorat *et al.* (1999) cannot be properly cited for teaching the amino acid sequence SEQ ID NO:8, as this is a teaching of the specification.

The teachings of US 6,455,267 do not help to identify the protein of Honnorat *et al.* (1996) as having amino acid sequence SEQ ID NO:8 or in identifying any nucleic acid that could encode a polypeptide with SEQ ID NO:8. Therefore, the combined teachings of Honnorat *et al.* (1996) as evidenced by Honnorat *et al.* (1999) in view of US Patent No. '267 cannot make obvious the invention of claims 3, 6 and 7.

With regard to claim 22, the Examiner has relied on the teachings of the present specification in combination with the other cited references to make the rejection. Before the present invention was described in the specification, one of ordinary skill in the art would not know the association of human ULIP4 with paraneoplastic neurological diseases, and would not have the necessary knowledge to provide a polypeptide comprising SEQ ID NO:8 or a fragment thereof as a component of a kit to test for binding of anti-CV2 antibodies. Citing Honnorat *et al.* (1999) in the rejection is not permissible, for reasons explained above. Honnorat *et al.* (1996) does not provide the

information necessary to identify a diffuse band of proteins as a single protein having SEQ ID NO:8. The teachings of US Patent No. 6,455,267 cannot provide any information to conceive of a kit for the diagnosis of paraneoplastic neurological syndromes, as it teaches nothing about PNS or any molecules associated with the pathology of PNS.

The Examiner cannot conclude that the band seen by Honnorat *et al.* (1996) on a polyacrylamide gel migrating at an apparent molecular weight of approximately 66 kDa consisted of one and only one protein that must have had amino acid SEQ ID NO:8. As reported in Honnorat *et al.* (1999) (see first paragraph of Discussion, pages 4230-4231, referring to the rat proteins) and in WO 02/02620 (see especially Table 1, page 5), the situation is far more complex. Ulip4 is one of a family of homologous proteins with molecular weights that could cause them to migrate on a polyacrylamide gel at an apparent molecular weight of approximately 66 kDa. The proteins could also be subject to post-translational processing, which results in further variation in an apparent molecular weight from a molecular weight predicted on the basis of amino acid sequence alone.

Anti-CV2 antibodies are not a preparation of monoclonal antibodies, nor are they antibodies that result from immunizing an animal with a purified protein. Anti-CV2 antibodies are autoantibodies present in serum of patients with paraneoplastic neurological syndrome. Anti-CV2 antibodies can bind to more than one protein. See Table 1, page 37 of the specification. cDNAs of rat proteins Ulip1, Ulip2, Ulip3 and Ulip4 were transfected into HeLa cells and the rat proteins produced in the HeLa cells were recognized by antibodies in sera from human patients. Note that one of the eight

sera tested contained antibodies that bound to rat Ulip1. Two of the eight sera tested contained antibodies that bound to rat Ulip3. One of ordinary skill in the art would be aware of the possibility of related proteins and cross-reactivity of antibodies, and would not rely on sera from patients to try to identify a protein, when the immunogen producing the antibodies in the sera had not been identified. This would be circular reasoning.

Honnorat *et al.* (1999) did not extract the band of proteins of approximately 66kDa from the gel of Honnorat *et al.* (1996), obtain the amino acid sequence of a protein, synthesize oligonucleotide primers based on the amino acid sequence and attempt to isolate a gene encoding a protein in the gel. With the limited information available, the Examiner is only speculating to identify the 66 kDa band of Honnorat (1996) as containing a protein having SEQ ID NO:8.

With regard to claims 15 and 33-35, the Examiner has stated (Office Action of 22 November 2004, page 31, lines 13-23):

> It would have been prima facie obvious to one ordinarily skilled in the art at the time of the invention to produce and use a kit comprising either the intact polypeptide disclosed by Honnorat *et al.* or an antigenic fragment thereof that binds anti-CV2 antibodies for use in detecting anti-CV2 antibodies and diagnosing a paraneoplastic neurological syndrome and tumor associated therewith in patients, because Honnorat *et al.* teaches detecting anti-CV2 antibodies is diagnostic of such disease and '267 teaches such diagnostic kits for use in detecting such autoantibodies. One ordinarily skilled in the art at the time the invention was made would have been motivated to make and use such kits to facilitate the diagnosis of a paraneoplastic neurological syndrome in which anti-CV2 antibodies are produced in patients and the tumor associated therewith.

Honnorat *et al.* (1996) defines anti-CV2 antibodies as those antibodies binding to a cytoplasmic antigen in a subpopulation of glial cells in the white matter (page 272, first paragraph of Results section). Honnorat *et al.* (1996) presents one experiment to test binding of antibodies in one human serum sample to human proteins in human brain

extracts. Serum from the patient contained antibodies that bound to a diffuse 66 kDa band in human brain extracts. See legend to Figure 7(B).

US Patent No. 6,455,267 describes the cloning of cDNA encoding glutamic acid decarboxylase (GAD) and the use of GAD protein in the identification of autoantibodies to GAD present in the sera of diabetic patients.

Combining the references Honnorat *et al.* (1996) and US 6,455,267, one of ordinary skill in the art might wish to develop an assay or assay kit to detect the antigen to which anti-CV2 antibodies bind. However, Honnorat *et al.* (1996) did not identify the brain protein to which anti-CV2 antibodies bind. Showing that there are proteins migrating at approximately 66 kDa in human brain extracts does not provide one of skill in the art with sufficient information to develop an assay or a kit to perform the assay. One of skill in the art would not be able to use the combined teachings of the references to produce a polypeptide comprising SEQ ID NO:8 or a fragment of such a polypeptide to use in a kit to detect anti-CV2 antibodies.

The Examiner has used Honnorat *et al.* (1999) for concluding that "fixed sections of human brain comprise an endogenous 66 kDa polypeptide, which comprises the amino acid sequences set forth as SEQ ID NO:8, to which anti-CV2 antibodies bind." The conclusion that the 66 kDa polypeptide has SEQ ID NO:8 is not a universal fact or a scientific truism, which in some circumstances, may be cited from a reference available as prior art after applicant's filing date. *In re Wilson*, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). See also MPEP § 2124.

Further, the citing of Honnorat *et al.* (1999) is not permissible for a second reason. Honnorat *et al.* (1999), published after the filing date of the application,

describes the work in the present specification. Thus, the Examiner is using the teachings of the application itself to support an allegation that a teaching in Honnorat *et al.* (1996) shows an inherent characteristic.

Based on the foregoing, Applicants respectfully request that the rejection to claims 3, 6, 7, 15, 22 and 33-35 under 35 U.S.C. § 103(a) be withdrawn.

In part 10 of the outstanding Office Action, the Examiner alleges that the application does not include an abstract of disclosure, as required by 37 C.F.R. § 1.72(b), alleging that the abstract is required to be on a separate sheet. Applicants respectfully submit that the present application is a national stage of a PCT application, which included an abstract of disclosure on the front page. In accordance with MPEP § 1893.03(e), the abstract of a PCT complies with the requirements of 37 C.F.R. § 1.72(b) and, therefore, it is improper to object to the present abstract of disclosure. Accordingly, Applicants respectfully request that the objection to the abstract be withdrawn.

In parts 11-12, the specification and drawing sheets/figures were objected to for not identifying that each of Figures 9-12 has four corresponding figure sheets. By this Amendment, Applicants have submitted replacement sheets for Figures 9-12, in which each is identified as having parts A-D, corresponding to each of the four sheets of each Figure, and Applicants have amended the specification to correspond accordingly, thereby obviating the objection to the brief description of the figures and the drawing sheets. Further, with regard to the Replacement Figure Sheets, the original French label of "souris" (Figures 9-11) has been changed to its English equivalent of "mouse" and "homme" (Figure 12) has been changed to "human" with subject matter basis for

the translation in the specification as filed on page 18, and, therefore, the correction is not new matter.

In part 13 of the Office Action, it was noted that the brief description of Figure 12 did not properly identify the subject matter of Figure 12 as corresponding to amino acid residues 1-55 and 57-553 of SEQ ID NO:8. By this Amendment, Applicants have amended the specification to obviate the objection.

In part 14, claim 10 was rejected under 35 U.S.C. § 112, first paragraph which, by this Amendment, Applicants have amended, thereby rendering the written description rejection now moot.

In part 16 of the Office Action, claim 4 was rejected under 35 U.S.C. § 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over Byk (database genEMBL Accession Number Y10976). The Byk reference is not prior art of the present application under 35 U.S.C. § 102(a), as the subject matter of claim 4 was disclosed in the French priority document, an English translation thereof and declaration of the translator is submitted herewith. Therefore, claim 4 is not anticipated by or obvious in view of Byk.

In view of the foregoing, Applicants respectfully submit that the present application is in condition for allowance.